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(54) Title: ACYLSEMICARBAZIDES AND THEIR USE AS CYCLIN DEPENDENT KINASE (CDK) INHIBITORS

(57) Abstract: The present invention realtes to the synthesis fo a new class of indeno [1,2-c]pyrazol-4-ones of formula (I): that are potent inhibitors of the class of enzymes known as cyclin dependent kinases, which relate to the catalytic subunits cdk1-9 and their regulatory subunits know as cyclins A-H. The invention also provides a novel method of treating cancer or otehr proliferative disease by administering a therapeutically effective amount of one of these compounds or a pharmaceutically acceptable salt form thereof. Alternatively, one can treat cancer or other proliferative disease by administering a therapeutically effective combination of one of the compounds of teh present invention and one or more other known anti-cancer or anti-proliferative agents.

TITLE

ACYLSEMICARBAZIDES AND THEIR USE AS CYCLIN DEPENDENT KINASE (CDK) INHIBITORS

FIELD OF THE INVENTION

This invention relates generally to novel 5-substituted-indeno[1,2-c]pyrazol-4-ones which are useful as cyclin dependent kinase (cdk) inhibitors, pharmaceutical compositions comprising the same, kits and methods for using the same for treating proliferative diseases, and intermediates and processes for making the same.

BACKGROUND OF THE INVENTION

One of the most important and fundamental processes in biology is the division of cells mediated by the cell cycle. This process ensures the controlled production of subsequent generations of cells with defined biological function. It is a highly regulated phenomenon and responds to a diverse set of cellular signals both within the cell and from external sources. A complex network of tumor promoting and suppressing gene products are key components of this cellular signaling process. Over expression of the tumor promoting components or the subsequent loss of the tumor suppressing products will lead to unregulated cellular proliferation and the generation of tumors (Pardee, Science 246:603-608, 1989).

Cyclin dependent kinases (cdks) play a key role in regulating the cell cycle machinery. These complexes consist of two components: a catalytic subunit (the kinase) and a regulatory subunit (the cyclin). To date, nine kinase subunits (cdk 1-9) have been identified along with several regulatory subunits (cyclins A-H)(A.M. Senderowicz and E.A. Sausville Journal of the National Cancer Institute (2000), 92 (5), 376-387; S. Mani; C. Wang; K. Wu; R. Francis; R.

Pestell Exp. Opin. Invest. Drugs (2000) 9(8), 1849-1870; Brizuela, Leonardo; Gyuris, Jeno; Mansuri, Muzammil, Princ. Mol. Oncol. (2000), 197-236; Fry, David W.; Garrett, Michelle Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs (2000), 2(1), 40-59).

Each kinase associates with a specific regulatory partner and together make up the active catalytic moiety. Each transition of the cell cycle is regulated by a particular cdk complex: G1/S by cdk2/cyclin E, cdk4/cyclin D1 and cdk6/cyclinD2; S/G2 by cdk2/cyclin A and cdk1/cyclin A; G2/M by cdk1/B. The coordinated activity of these kinases guides the individual cells through the replication process and ensures the vitality of each subsequent generation (Sherr, Cell 73:1059-1065, 1993; Draetta, Trends Biochem. Sci. 15:378-382, 1990)

An increasing body of evidence has shown a link between tumor development and cdk related malfunctions. Over expression of the cyclin regulatory proteins and subsequent kinase hyperactivity have been linked to several types of cancers (Jiang, Proc. Natl. Acad. Sci. USA 90:9026-9030, 1993; Wang, Nature 343:555-557, 1990). More recently, endogenous, highly specific protein inhibitors of cdks were found to have a major affect on cellular proliferation (Kamb et al, Science 264:436-440, 1994; Beach, Nature 336:701-704, 1993). These inhibitors include $p16^{INK4}$ (an inhibitor of cdk4/D1), $p21^{CIP1}$ (a general cdk inhibitor), and $p27^{KIP1}$ (a specific cdk2/E inhibitor). A recent crystal structure of p27 bound to cdk2/A revealed how these proteins effectively inhibit the kinase activity through multiple interactions with the cdk complex (Pavletich, Nature 382:325-331, 1996). These proteins help to regulate the cell cycle through specific interactions with their corresponding cdk complexes. Cells deficient in these inhibitors are prone to unregulated growth and tumor formation.

Protein kinases, in particular, CDK, play a role in the regulation of cellular proliferation. Therefore, CDK inhibitors could be useful in the treatment of cell proliferative disorders such as cancer, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, fungal infections, endotoxic shock, trasplantaion rejection, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis (U.S. Patent No. 6,114,365).

CDKs are also known to play a role in apoptosis. Therefore CDK inhibitors, could be useful in the treatment of useful of cancer; viral infections, for example, herpevirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus; prevention of AIDS development in HIV-infected individuals; autoimmune diseases, for example, systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; neurodegenerative disorders, for example, Alzheimer's disease, AIDS-relateddementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration; myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain (U.S. Patent No. 6,107,305).

It has also been discovered that some cyclin-dependent kinase inhibitors can be used in combination therapy with other anticancer agents. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor, flavopiridol, has been used with other anticancer agents in

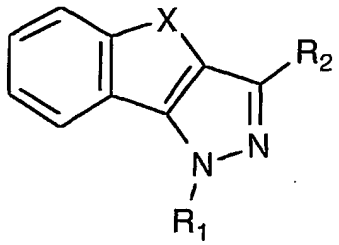
cancer combination therapy. Cancer Research, 57, 3375 (1997).

Also, it has recenly been disclosed that CDK inhibitors may be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse (U.S. Patent No. 6,107,305).

Furthermore, it has recently been discovered that cdk5 is involved in the phosphorylation of tau protein, and therefore CDK inhibitors may be useful in the treatment of Alzheimer's disease (J. Biochem., 117, 741-749, 1995).

This body of evidence has led to an intense search for small molecule inhibitors of the cdk family as an approach to cancer chemotherapy. There are no known examples of molecules related to the current invention which describe 5-substituted-indeno[1,2-c]pyrazoles as cdk inhibitors. There is one case describing indeno[1,2-c]pyrazoles having anticancer activity. There are two other examples which describe indeno[1,2-c]pyrazoles having unrelated utilities and structures.

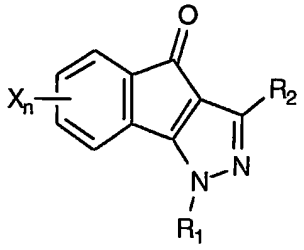
A series of indeno[1,2-c]pyrazoles having anticancer activity are described in JP 60130521 and JP 62099361 with the following generic structure:



No substitution is claimed on the indenophenyl portion of the molecule and the molecules are not indicated to be cdk

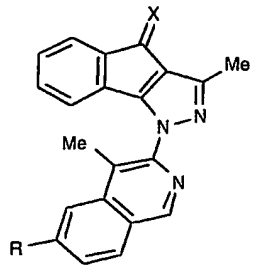
inhibitors. In addition, we discovered that substitution at the 5-position was critical for cdk inhibitory activity.

A series of indeno[1,2-c]pyrazoles having herbicidal activity are described in GB 2223946 with the following generic structure:



wherein X_n is defined as halo, alkyl, haloalkyl, and haloalkoxy; n = 0-2. In addition, R_1 is defined as acyl and R_2 is defined as alkyl or cycloalkyl.

A series of 1-(6'-substituted-4'-methylquinol-2'-yl)-3-methylindeno[1,2-c]pyrazoles having CNS activity are described by Quraishi, Farmaco 44:753-8, 1989 with the following generic structure:



Compounds of this series are not considered to be part of the presently claimed invention.

SUMMARY OF THE INVENTION

The present invention describes a novel class of indeno[1,2-c]pyrazol-4-ones or pharmaceutically acceptable

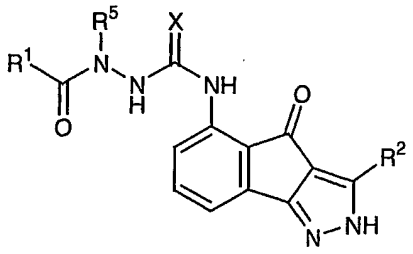
salt forms thereof that are potent inhibitors of the class of enzymes known as cyclin dependent kinases, which relate to the catalytic subunits cdk 1-9 and their regulatory subunits known as cyclins A-H.

It is another object of this invention to provide a novel method of treating proliferative diseases associated with CDK activity by administering a therapeutically effective amount of one of the compounds of the invention or a pharmaceutically acceptable salt form thereof.

It is another object of this invention to provide a novel method of treating cancer associated with CDK activity by administering a therapeutically effective amount of one of the compounds of the invention or a pharmaceutically acceptable salt form thereof.

It is another object of this invention to provide a novel method of treating a proliferative disease, which comprises administering a therapeutically effective combination of one of the compounds of the present invention and one or more other known anti-cancer treatments such as radiation therapy, chemotoxic or chemostatic agents.

These and other objectives have been achieved by the inventors' discovery that compounds of formula (I):



(I)

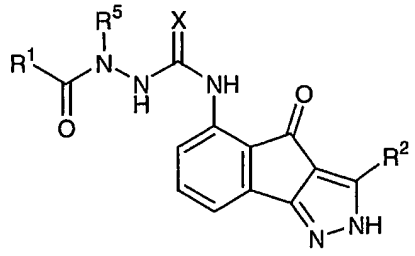
wherein R^1, R^2, R^5 and X are defined below or pharmaceutically acceptable salts thereof are cyclin dependent kinase inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention pertains to novel cyclin dependent kinase inhibitors (cdks) and specifically, but not exclusively, as inhibitors of cdk/cyclin complexes. The inhibitors of this invention are indeno[1,2-c]pyrazol-4-one analogs. Certain analogs were selective for their activity against cdks and their cyclin bound complexes and were less active against other known serine/threonine kinases such as Protein Kinase A (PKA) and Protein Kinase C (PKC).

As described herein, the inhibitors of this invention are capable of inhibiting the cell-cycle machinery and consequently would be useful in modulating cell-cycle progression, which would ultimately control cell growth and differentiation. Such compounds would be useful for treating subjects having disorders associated with excessive cell proliferation, such as the treatment of cancer, psoriasis, immunological disorders involving unwanted leukocyte proliferation, in the treatment of restinosis and other smooth muscle cell disorders, and the like.

(1) The present invention, in a first embodiment, describes a novel compound of formula (I):



X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C_{1-4} alkyl substituted with 1-3 R^4, C_{5-10} alkyl substituted with 0-3 R^4, C_2-C_{10} alkenyl substituted with 0-3 R^4, C_2-C_{10} alkynyl substituted with 0-3 R^4, C_3-C_{10} carbocycle substituted with 0-5 R^6, or 5-10 membered heterocycle substituted with 0-3 R^6; provided that if R^1 is phenyl or benzyl, then R^1 is substituted with 1-5 R^6;

R^2 is H, C_{1-10} alkyl substituted with 0-3 R^7, C_{2-10} alkenyl substituted with 0-3 R^7, C_{2-10} alkynyl substituted with 0-3 R^7, $-CF_3$, C_{3-10} carbocycle substituted with 0-5 R^8, or 3-10 membered heterocycle substituted with 0-5 R^8;

R^3 and R^{3a} are independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^4 and R^7 are, at each occurance, independently selected from the group: halo, -CN, NO_2, $-NR^9R^{9a}$, $NR^9NR^{9a}R^{9b}$, $NR^9C(O)OR^{10}$, $NR^9C(O)R^{10}$, =O, OR^{10}, SR^{10}, -CF3, COR^{10}, CO_2R^{10}, $CONR^9R^{9a}$, $NHC(O)NR^9R^{9a}$, $NHC(S)NR^9R^{9a}$, $SO_2NR^9R^{9a}$, SO_2R^{10}, C_{3-10} carbocycle substituted with 0-5 R^{11}, and 5-10 membered heterocycle substituted with 0-3 R^{11};

R^5 is selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^6 and R^8 are, at each occurance, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$,

$SO_2NR^{13}R^{13a}$, SO_2R^{14}, C_{3-10} carbocycle substituted with 0-5 R^{15}, and 5-10 membered heterocycle substituted with 0-3 R^{15}, or when two R^{6s} or R^{8s} are attachd to two adjacent carbon atoms, the two R^{6s} or R^{8s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$;

R^9 is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{9b} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl; or

R^9 and R^{9a}, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R^{16};

R^{9a} is selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{10}, R^{14}, R^{17} are, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl, benzyl;

R^{11} is, at each occurance, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{18}R^{18a}$, $NR^{18}NR^{18a}R^{18b}$, $NR^{18}C(O)OR^{17}$, $NR^{18}C(O)R^{17}$, =O, OR^{17}, SR^{17}, COR^{17}, CO_2R^{17}, $CONR^{18}R^{18a}$, $NHC(O)NR^{18}R^{18a}$, $NHC(S)NR^{18}R^{18a}$, $SO_2NR^{18}R^{18a}$, SO_2R^{17}, C_{3-10} carbocycle substituted with 0-5 R^{19}, and 5-10 membered heterocycle substituted with 0-3 R^{19};

R^{13} is is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{13a} is, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; or

R^{13} and R^{13a}, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R^{16};

R^{13b} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{15}, R^{16} and R^{19} are, at each occurance, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{20}R^{20a}$, $NR^{20b}NR^{20}R^{20a}$, $NR^{20}C(O)OR^{21}$, $NR^{20}C(O)R^{21}$, =O, OR^{21}, SR^{21}, COR^{21}, CO_2R^{21}, $CONR^{20}R^{20a}$, $NHC(O)NR^{20}R^{20a}$, $NHC(S)NR^{20}R^{20a}$, $SO_2NR^{20}R^{20a}$, SO_2R^{21}, or when two R^{15}s, R^{16}s or R^{19}s are attachd to two adjacent carbon atoms, the two R^{15}s R^{16}s or R^{19}s may combine to form -OCH2O- or -OCH2CH2O-;

R^{18} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{18a} is, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;or

R^{18} and R^{18a}, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R^{19};

R^{18b} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl; or

R^{20} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{20a} is, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{20b} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl; and

R^{12} and R^{21} are, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl, benzyl; or

a pharmaceutically acceptable salt form thereof, a pharmaceutically acceptable prodrug form thereof, an N-oxide form thereof, or a stereoisomer thereof.

(2) Another embodiment of the invention is a compound of embodiment (1) wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4, C_2-C_4 alkenyl substituted with 0-3 R^4, C_2-C_4 alkynyl substituted with 0-3 R^4, C_3-C_{10} carbocycle substituted with 0-5 R^6, or 5-10 membered heterocycle substituted with 0-3 R^6.

(3) Another embodiment of the invention is a compound of embodiment (1) wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4, C_2-C_4 alkenyl substituted with 0-3 R^4, C_2-C_4 alkynyl substituted with 0-3 R^4, C_3-C_6 carbocycle substituted with 0-5 R^6, or 5-7 membered heterocycle substituted with 0-3 R^6.

(4) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^1 is C_3-C_6 saturated carbocycle substituted with 0-5 R^6, or 5-7 membered saturated heterocycle substituted with 0-3 R^6.

(5) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^1 is C_5-C_6 partially saturated carbocycle substituted with 0-5 R^6, or 5-7 membered partially saturated heterocycle substituted with 0-3 R^6.

(6) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^1 is phenyl substituted with 1-5 R^6, naphthyl substituted with 0-5 R^6, or 5-6 membered aromatic heterocycle substituted with 0-3 R^6.

(7) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^1 is phenyl substituted with 1-3 R^6, naphthyl substituted with 0-3 R^6, or 5-6 membered aromatic heterocycle substituted with 0-3 R^6.

(8) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^1 is C_3-C_{10} carbocycle substituted with 0-5 R^6, or 5-10 membered heterocycle substituted with 0-3 R^6;

R^6 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14}, or when two R^{6s} are attached to two adjacent carbon atoms, the two R^{6s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$.

(9) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^6 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14}, or when two R^{6s} are attached to two adjacent carbon atoms, the two R^{6s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$;

R^{13}, R^{13a} and R^{13b} are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; and

R^{14} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl, and benzyl.

(10) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^6 is independently at each occurrence selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14};

R^{13}, R^{13a} and R^{13b} are each independently selected from the group: H or methyl;and

R^{14} is independently selected from the group: H, methyl, phenyl, and benzyl.

(11) Another embodiment of the invention is a compound of embodiment (1) wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4;

R^4 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, $-NR^9R^{9a}$, $NR^9NR^{9a}R^{9b}$, $NR^9C(O)OR^{10}$, $NR^9C(O)R^{10}$, =O, OR^{10}, SR^{10}, -CF3, COR^{10}, CO_2R^{10}, $CONR^9R^{9a}$, $NHC(O)NR^9R^{9a}$, $NHC(S)NR^9R^{9a}$, $SO_2NR^9R^{9a}$, and SO_2R^{10};

R^9 is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9a} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9b} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; or

R^9 and R^{9a}, together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3 R^{16};

R^{16} is, at each occurrence, independently selected from the group consisting of: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{20}R^{20a}$, $NR^{20b}NR^{20}R^{20a}$, $NR^{20}C(O)OR^{21}$, $NR^{20}C(O)R^{21}$, =O, OR^{21}, SR^{21}, COR^{21}, CO_2R^{21}, $CONR^{20}R^{20a}$, $NHC(O)NR^{20}R^{20a}$, $NHC(S)NR^{20}R^{20a}$, $SO_2NR^{20}R^{20a}$, and SO_2R^{21}; and

R^{20}, R^{20a}, and R^{20b} are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl.

(12) Another embodiment of the invention is a compound of embodiment (1) wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4;

R^3 and R^{3a} are independently selected from the group: H, methyl, phenyl and benzyl;

R^4 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, $-NR^9R^{9a}$, $NR^9NR^{9a}R^{9b}$, $NR^9C(O)OR^{10}$, $NR^9C(O)R^{10}$, =O, OR^{10}, SR^{10}, -CF3, COR^{10}, CO_2R^{10}, $CONR^9R^{9a}$, $NHC(O)NR^9R^{9a}$, $NHC(S)NR^9R^{9a}$, $SO_2NR^9R^{9a}$, SO_2R^{10}, C_{3-10} carbocycle substituted with 0-5 R^{11}, and 5-10 membered heterocycle substituted with 0-3 R^{11};

R^9 is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9a} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9b} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{10} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl, benzyl; and

R^{11} is, at each occurrence, independently selected from the group consisting of: selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{18}R^{18a}$, $NR^{18}NR^{18a}R^{18b}$, $NR^{18}C(O)OR^{17}$, $NR^{18}C(O)R^{17}$, =O, OR^{17}, SR^{17}, COR^{17}, CO_2R^{17}, $CONR^{18}R^{18a}$, $NHC(O)NR^{18}R^{18a}$, $NHC(S)NR^{18}R^{18a}$, $SO_2NR^{18}R^{18a}$, SO_2R^{17}, C_{3-10} carbocycle substituted with 0-5 R^{19}, and 5-10 membered heterocycle substituted with 0-3 R^{19}.

(13) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^2 is C_{1-4} alkyl substituted with 0-3 R^7, C_{2-4} alkenyl substituted with 0-3 R^7, C_{2-4} alkynyl substituted with 0-3 R^7, $-CF_3$, C_{3-6} carbocycle substituted with 0-5 R^8, or 3-7 membered heterocycle substituted with 0-5 R^8.

(14) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^2 is C_{1-4} alkyl substituted with 0-3 R^7, C_{2-4} alkenyl substituted with 0-3 R^7, C_{2-4} alkynyl substituted with 0-3 R^7, $-CF_3$, C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8.

(15) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^2 is C_{3-6} saturated carbocycle substituted with 0-5 R^8, or 5-7 membered saturated heterocycle substituted with 0-5 R^8.

(16) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^2 is C_{5-6} partially saturated carbocycle substituted with 0-5 R^8, or 5-7 membered partially saturated heterocycle substituted with 0-5 R^8.

(17) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^2 is phenyl substituted with 0-5 R^8, naphthyl substituted with 0-5 R^8 or or 5-6 membered aromatic heterocycle heterocycle substituted with 0-5 R^8.

(18) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^2 is phenyl substituted with 0-3 R^8, naphthyl substituted with 0-3 R^8 or or 5-6 membered aromatic heterocycle heterocycle substituted with 0-3 R^8.

(19) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^2 is C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8;

R^8 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14}, or when two R^{8s} are attachd to two adjacent carbon atoms, the two R^{8s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$; and

R^{13} R^{13a}, and R^{13b} are are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; or

R^{13} and R^{13a}, together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3 R^{16}.

(20) Another embodiment of the invention is a compound of embodiment (1) wherein:

R^2 is C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8;

R^8 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O,

OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, SO_2R^{14}, C_{3-10} carbocycle substituted with 0-5 R^{15}, and 5-10 membered heterocycle substituted with 0-3 R^{15},or when two R^{8s} are attachd to two adjacent carbon atoms, the two R^{8s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$;

R^{13} R^{13a}, and R^{13b} are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; and

R^{15} is, at each occurrence, independently selected from the group consisting of: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{20}R^{20a}$, $NR^{20b}NR^{20}R^{20a}$, $NR^{20}C(O)OR^{21}$, $NR^{20}C(O)R^{21}$, =O, OR^{21}, SR^{21}, COR^{21}, CO_2R^{21}, $CONR^{20}R^{20a}$, $NHC(O)NR^{20}R^{20a}$, $NHC(S)NR^{20}R^{20a}$, $SO_2NR^{20}R^{20a}$, and SO_2R^{21}, or when two R^{15}s, are attachd to two adjacent carbon atoms, the two R^{15}s may combine to form -OCH2O- or -OCH2CH2O-.

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (13).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (14).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (15).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (16).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (17).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (18).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (19).

A more preferred embodiment, is a compound according to any of embodiments (2) to (12) further comprising embodiment (20).

In a most preferred embodiment, the compounds of formula (I) are selected from:

3-(4-methoxyphenyl)-5-(2-(3,5-dimethoxybenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-isonicotinoyl hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-nictinoylhydrazinecarbox amido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-hydroxybenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-aminobenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-aminobenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-aminobenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-N,N-dimethylaminobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-methoxybenzoylhydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-hydroxybenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one; and

3-(4-methoxyphenyl)-5-(2-(3,5-diaminobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(1-naphthoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-amido hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-phenylamido hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-methylbenzoyl hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-naphthoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-(4-hydroxyphenyl)propionyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-methoxybenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-thienoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-methylbenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-amino-4-hydroxybenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2,5-dichlorobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-piperazinylphenyl)-5-(2-(nicotinoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(nicotinoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(isonicotinoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-piperazinylphenyl)-5-(2-(isonicotinoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one; and

3-(4-piperazinylphenyl)-5-(2-(3,5-dimethoxybenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one; or a pharmaceutically acceptable salt form thereof, a pharmaceutically acceptable prodrug form thereof, an N-oxide form thereof, or a stereoisomer thereof.

Another embodiment of the present invention is a pharmaceutical composition comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I).

Another embodiment of the present invention is a method of treating a proliferative disease associated with CDK activity comprising: administering to a host in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically effective salt form thereof.

Another embodiment of the present invention is a method of treating a cell proliferative disease associated with CDK activity in a patient,comprising administrering to said patient a pharmaceutically effective amount of a compound of

formula (I), wherein the proliferative diseases is selected from the group consisting of: Alzheimer's disease, viral infections, auto-immune diseases, fungal disease, cancer, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis, neurodegenerative disorders and post-surgical stenosis and restenosis.

Another embodiment of the present invention is a method of treating cancer associated with CDK activity in a patient,comprising administrering to said patient a pharmaceutically effective amount of a compound of formula (I), wherein the cancer is selected from the group consisting of: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Another embodiment of the present invention is a method of treating a disease associated with apoptosis in a patient,comprising administrering to said patient a pharmaceutically effective amount of a compound of formula (I), wherein the disease associated with apoptosis is

selected from the group consisting of: cancer, viral infections, autoimmune diseases and neurodegenerative disorder.

Another embodiment of the present invention is a method of inhibiting tumor angiogenesis and metastasis in a patient,comprising administrering to said patient a pharmaceutically effective amount of a compound of formula (I).

Another embodiment of the present invention is a method of treating a disease associated with protein kinase activity in a patient,comprising administrering to said patient a pharmaceutically effective amount of a compound of formula (I), wherein the protein kinase is selected from the group consisting of: e.g. protein kinase C, her2, rafl, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, weel kinase, Src, and Abl.

Another embodiment of the present invention is a method of modulating the level of cellular RNA and DNA synthesis in a patient, comprising administering to said patient a CDK inhibitory effective amount of a compound of formula (I).

Another embodiment of the present invention is a method of treating viral infections in a patient, comprising administering to said patient a CDK inhibitory effective amount of a compound of formula (I), wherein the viral infections is selected from the group consiting of HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus.

Another embodiment of the present invention is a method of chemopreventing cancer in a patient, comprising administering to said patient a CDK inhibitory effective amount of a compound of formula (I).

Another embodiment of the present invention is a method of inhibiting CDK activity comprising combining an effective amount of the compound of formula (I) with a composition containing CDK.

Another embodiment of the present invention is a method of treating cancer associated with CDK activity in a patient,comprising administrering to said patient a pharmaceutically effective amount of a compound of formula (I) in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, such as for example, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methoxtrexate.

Another embodiment of the present invention is a method treating proliferative diseases associated with CDK activity, in a patient,comprising administrering to said patient a pharmaceutically effective amount of a compound of formula (I), in combination (administered together or sequentially) with known anti-proliferating agents selected from the group consisting of:, altretamine, busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, thiotepa, cladribine, fluorouracil, floxuridine, gemcitabine, thioguanine, pentostatin, methotrexate, 6-mercaptopurine, cytarabine, carmustine, lomustine, streptozotocin, carboplatin, cisplatin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, JM216, JM335, fludarabine, aminoglutethimide, flutamide, goserelin, leuprolide, megestrol acetate, cyproterone acetate, tamoxifen, anastrozole, bicalutamide, dexamethasone, diethylstilbestrol, prednisone, bleomycin, dactinomycin, daunorubicin, doxirubicin, idarubicin, mitoxantrone, losoxantrone, mitomycin-c, plicamycin, paclitaxel, docetaxel, CPT-11, epothilones , topotecan, irinotecan, 9-amino camptothecan, 9-nitro camptothecan, GS-211, etoposide,

teniposide, vinblastine, vincristine, vinorelbine, procarbazine, asparaginase, pegaspargase, methoxtrexate, octreotide, and estramustine, hydroxyurea.

Another embodiment of the present invention is a method of inhibiting CDK1 activity, comprising adminsitering to a patient in need thereof an efective CDK1 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK2 activity, comprising adminsitering to a patient in need thereof an efective CDK2 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK3 activity, comprising adminsitering to a patient in need thereof an efective CDK3 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK4 activity, comprising adminsitering to a patient in need thereof an efective CDK4 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK5 activity, comprising adminsitering to a patient in need thereof an efective CDK5 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK6 activity, comprising adminsitering to a patient in need thereof an efective CDK6 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK7 activity, comprising adminsitering to a

patient in need thereof an efective CDK7 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK8 activity, comprising adminsitering to a patient in need thereof an efective CDK8 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

Another embodiment of the present invention is a method of inhibiting CDK9 activity, comprising adminsitering to a patient in need thereof an efective CDK9 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

It is a further object of the invention to provide a pharmaceutical kit for combination treatment of proliferative diseases associated with CDK activity, said kit comprising a plurality of separate containers, wherein at least one of said containers contains a compound of formula (I), and at least another of said containers contains one or more compounds selected from the group consisting of altretamine, busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, thiotepa, cladribine, fluorouracil, floxuridine, gemcitabine, thioguanine, pentostatin, methotrexate, 6-mercaptopurine, cytarabine, carmustine, lomustine, streptozotocin, carboplatin, cisplatin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, JM216, JM335, fludarabine, aminoglutethimide, flutamide, goserelin, leuprolide, megestrol acetate, cyproterone acetate, tamoxifen, anastrozole, bicalutamide, dexamethasone, diethylstilbestrol, prednisone, bleomycin, dactinomycin, daunorubicin, doxirubicin, idarubicin, mitoxantrone, losoxantrone, mitomycin-c, plicamycin, paclitaxel, docetaxel, CPT-11, epothilones , topotecan, irinotecan, 9-amino camptothecan, 9-nitro camptothecan, GS-211, etoposide,

teniposide, vinblastine, vincristine, vinorelbine, procarbazine, asparaginase, pegaspargase, methoxtrexate, octreotide, and estramustine, hydroxyurea, and said containers optionally contain a pharmaceutical carrier.

It is a further object of the invention to provide a method of treating a patient having a disorder associated with excessive cell proliferation, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), such that the excessive cell proliferation in the patient is reduced.

It is appreciated that certain feactures of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various feactures of the invention which are, for brevity, described in the context of a single embodiment, may also be provided seperately or in any suitable subcombination.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

Definitions

As used herein, the following terms and expressions have the indicated meanings.

The term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of the invention as hereinbefore described i.e. compounds of formula (I), which expression includes the prodrugs thereof, N-oxides thereof, the pharmaceutically acceptable salts thereof, and the solvates thereof, e.g. hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

The term "derivative" means a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an amine.

The term "effective amount" means an amount of a compound/composition according to the present invention effective in producing the desired therapeutic effect.

The term "amine protecting group" means an easily removable group which is known in the art to protect an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of amine protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, for example, T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Preferred amine protecting groups are acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethxoycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 1,1-dimethylpropynyloxycarbonyl, benzyloxycarbonyl (CBZ), p-nitrobenzyloxycarbony, 2,4-dichlorobenzyloxycarbonyl, and the like.

The term "acid labile amine protecting group" means an amine protecting group as defined above which is readily removed by treatment with acid while remaining relatively

stable to other reagents. A preferred acid labile amine protecting group is *tert*-butoxycarbonyl (BOC).

The term "hydrogenation labile amine protecting group" means an amine protecting group as defined above which is readily removed by hydrogenation while remaining relatively stable to other reagents. A preferred hydrogenation labile amine protecting group is benzyloxycarbonyl (CBZ).

The term "hydrogenation labile acid protecting group" means an acid protecting group as defined above which is readily removed by hydrogenation while remaining relatively stable to other reagents. A preferred hydrogenation labile acid protecting group is benzyl.

The term "analogue" means a compound which comprises a chemically modified form of a specific compound or class thereof, and which maintains the pharmaceutical and/or pharmacological activities characteristic of said compound or class.

The term "patient" includes both human and other mammals.

The term "pharmaceutical composition" means a composition comprising a compound of formula (I) and at least one component selected from the group comprising pharmaceutically acceptable carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Examples of suspending agents include ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents,

for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monosterate and gelatin. Examples of suitable carriers, diluents, solvents or vehicles include water, ethanol, polyols, suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Examples of excipients include lactose, milk sugar, sodium citrate, calcium carbonate, dicalcium phosphate phosphate. Examples of disintegrating agents include starch, alginic acids and certain complex silicates. Examples of lubricants include magnesium stearate, sodium lauryl sulphate, talc, as well as high molecular weight polyethylene glycols.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanolates, methanolates, and the like.

The term "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. In addition, the term is intended to include both unsubstituted and substituted alkyl groups, the latter referring to alkyl moieties having one or more hydrogen substituents replaced by, but not limited to halogen, hydroxyl, carbonyl, alkoxy, ester, ether, cyano, phosphoryl,

amino, imino, amido, sulfhydryl, alkythio, thioester, sulfonyl, nitro, heterocyclo, aryl or heteroaryl. It will also be understood by those skilled in the art that the substituted moieties themselves can be substituted as well when appropriate.

The term "alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 10 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 8 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, and decenyl.

The term "alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 10 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 8 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. Exemplary alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl and decynyl.

The terms "halo" or "halogen" as used herein refer to fluoro, chloro, bromo and iodo. The term "aryl" is intended to mean an aromatic moiety containing the specified number of carbon atoms, such as, but not limited to phenyl, indanyl or naphthyl. The terms "cycloalkyl" and "bicycloalkyl" are intended to mean any stable ring system, which may be saturated or partially unsaturated. Examples of such include, but are not limited to, cyclopropyl, cyclopentyl,

cyclohexyl, norbornyl, bicyclo[2.2.2]nonane, adamantly, or tetrahydronaphthyl (tetralin).

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl,; [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than

1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl,

quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-

acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, the disclosure of which is hereby incorporated by reference.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

The term "Pharmaceutically acceptable prodrugs" as used herein means those prodrugs of the compounds useful according to the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

The term "Prodrugs", as the term is used herein, are intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (i.e., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same, and compositions containing the same. Prodrugs of the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. The transformation in vivo may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfydryl group, respectively. Functional groups which may be rapidly transformed, by metabolic cleavage, in vivo form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds

useful according to this invention are cleaved in vivo, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion of prodrugs is provided in the following: Design of Prodrugs, H. Bundgaard, ed., Elsevier, 1985; Methods in Enzymology, K. Widder et al, Ed., Academic Press, 42, p.309-396, 1985; A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design and Applications of Prodrugs" p.113-191, 1991; Advanced Drug Delivery Reviews, H. Bundgard, 8, p.1-38, 1992; Journal of Pharmaceutical Sciences, 77, p. 285, 1988; Chem. Pharm. Bull., N. Nakeya et al, 32, p. 692, 1984; Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, Vol. 14 of the A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein by reference.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

The term "Treating" refers to:

(i) preventing a disease, disorder or condition from occurring in an animal which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and
(iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

Preparation of Compounds of the Invention

It will be apparent to those skilled in the art that certain compounds of formula (I) can exhibit isomerism, for example geometrical isomerism, e.g., E or Z isomerism, and optical isomerism, e.g., R or S configurations. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl moieties. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

Where the compound of the present invention is substituted with a basic moiety, acid addition salts are formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically

acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on CDK inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures.

According to a further feature of the invention, acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The compounds of this invention can be regenerated from their corresponding acid addition salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid

form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on CDK inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as

tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The compounds of this invention can be regenerated from their corresponding base addition salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

Pharmaceutically acceptable salts also include quaternary lower alkyl ammonium salts. The quaternary salts are prepared by the exhaustive alkylation of basic nitrogen atoms in compounds, including nonaromatic and aromatic basic nitrogen atoms, according to the invention, i.e., alkylating the non-bonded pair of electrons of the nitrogen moieties with an alkylating agent such as methylhalide, particularly methyl iodide, or dimethyl sulfate. Quaternarization results in the nitrogen moiety becoming positively charged and having a negative counter ion associated therewith.

As will be self-evident to those skilled in the art, some of the compounds of this invention do not form stable salts. However, acid addition salts are more likely to be formed by compounds of this invention having a nitrogen-containing heteroaryl group and/or wherein the compounds contain an amino group as a substituent. Preferable acid addition salts of the compounds of the invention are those wherein there is not an acid labile group.

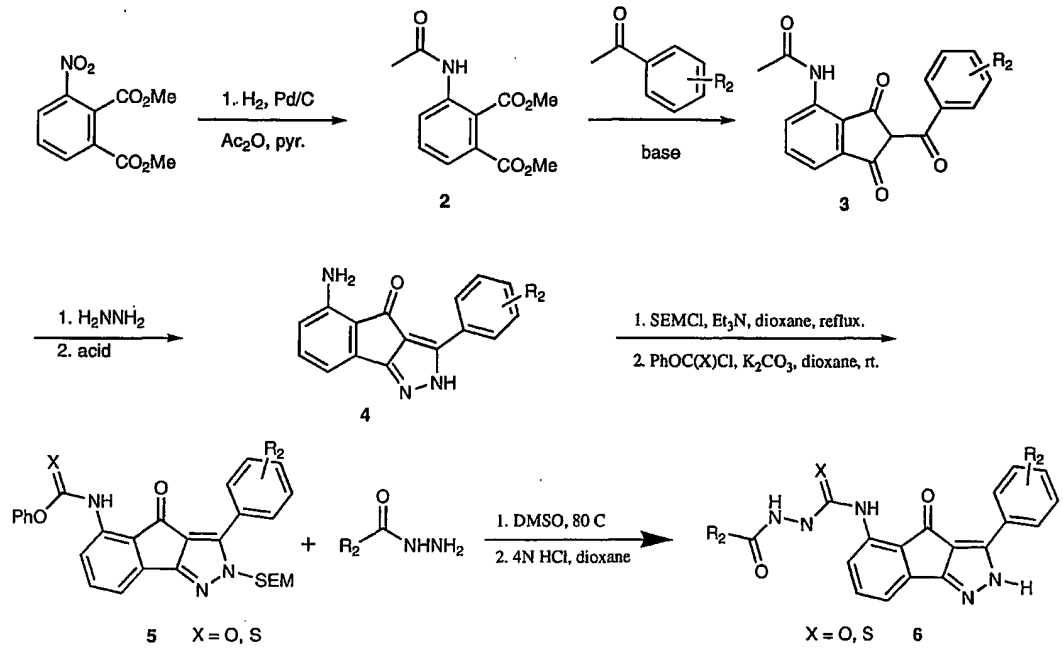
As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

Compounds according to the invention, for example, starting materials, intermediates or products, are prepared as described herein or by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R. C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Green and P.G.M.Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991; J. F. W. McOmie in "Protective Groups in Organic Chemistry" Plenum Press, 1973.

Preferred methods of synthesizing the compounds of the invention include, but are not limited to, those methods described below. Each of the references cited below are hereby incorporated herein by reference.

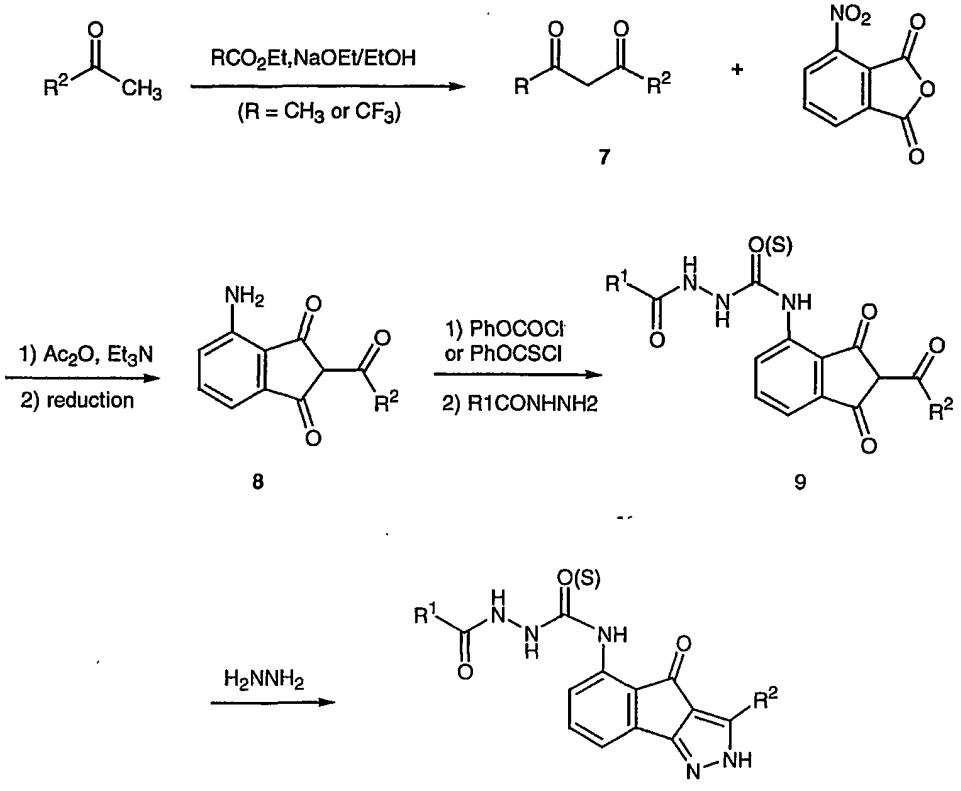
Scheme 1



An approach to preparing indeno[1,2-c]pyrazol-4-ones is presented in Scheme 1 and can be used to prepare compounds of the present invention. The nitro group of dimethyl 3-nitrophthalate was reduced to the amine using catalytic hydrogenation. The aniline was acylated using acetic anhydride and pyridine as a base. A mixture of the resulting acetamide 2 and an acetophenone were treated with a strong base in an appropriate solvent at elevated temperature to give the desired triketone 3. Additional means of preparing triketones are known to one skilled in the art as described in Kilgore et al, Industrial and Engineering Chemistry 34:494-497, 1946, the contents of which are hereby incorporated herein by reference. The triketone was treated with hydrazine at elevated temperature in an appropriate solvent to give the indeno[1,2-c]pyrazol-4-one ring system. Additional means of preparing indeno[1,2-c]pyrazol-4-ones are known to one skilled in the art as described in Lemke et al., J. Heterocyclic Chem. 19:1335-1340, 1982; Mosher and

Soeder, J. Heterocyclic Chem. 8:855-59, 1971; Hrnciar and Svanygova Collect. Czech. Chem. Commun. 59:2734-40, 1994 the contents of which are hereby incorporated herein by reference. The amide was deacylated by heating with a strong acid in an appropriate solvent to give aniline 4. Treating the intermediate 5-aminoindeno[1,2-c]pyrazol-4-one (4) with 2-(trimethylsilyl) ethoxymethylmethyl chloride (SEMCl) and a suitable base in an inert solvent under reflux gives the SEM protected intermediate. The aniline is converted to the carbamate 5 using methods known to those skilled in the art. This intermediate is reacted with carbazates in DMSO at elevated temperatures and then the SEM group is removed by treating with acid in a polar protic solvent to give the desired acylsemicarbazide-containing indenopyrazole analogs 6.

Scheme 2



Another method for preparing the triketones 3 of Scheme 1 employs the condensation of a 1,3-diketone 7 with 3-nitrophthalic anhydride as described in Rotberg and Oshkaya, Zh. Organ. Khim. 8:84-87, 1972; Zh. Organ. Khim. 9:2548-2550, 1973, the contents of which are hereby incorporated herein by reference. The 1,3-diketones, when not commercially available can be readily prepared by one skilled in the art by the acetylation or trifluoroacetylation of the requisite methyl ketone, R^1COCH_3. Reduction of the nitro derivative to the aniline 8 can be accomplished in a variety of ways including catalyic hydrogenation, treatment with zinc or iron under acidic conditions, or treatment with other reducing agents such as sodium dithionite or stannous chloride. Acetylation of the aniline 8 provides the triones 3.

Alternatively, the indeno[1,2-c]pyrazol-4-ones of this invention can be prepared as shown in Scheme 2. Exposure of aniline 8 to phenyl chloroformate or phenyl chlorothionoformate in the presence of base, followed by treatment of the intermediate with the appropriate carbazate, provides either trione 9, a hydrazone of 9, or mixtures of 9 and its hydrazone. When 9 or its hydrazone is allowed to react with hydrazine as described above the pyrazoles 10 are obtained.

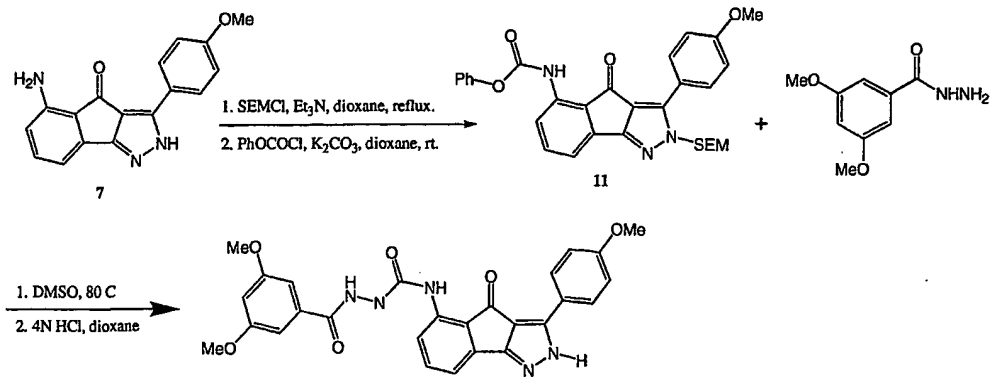
Other features of the invention will become apparent during the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Examples

Abbreviations used in the Examples are defined as follows: "°C" for degrees Celsius, "CIMS" for chemical ionization mass spectroscopy, "eq" for equivalent or equivalents, "g" for gram or grams, "h" for hour or hours, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "mmol" for millimolar, "M" for molar, "min" for minute or minutes, "p-TsOH" for para-toluenesulphonic acid, "DMF" for dimethylformamide, and "TFA" for trifluoroacetic acid.

Example I

Preparation of 3-(4-methoxyphenyl)-5-(2-(3,5-dimethoxybenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one



Step 1. Synthesis of 11 from 7.

The synthesis for the starting aniline is this example is described in WO 9954308 and is incorporated herein by reference. A suspension of aniline 7 (0.5 g, 1.7 mmol) in dioxane (10 mL) was treated with triethylamine (0.48 mL, 3.4 mmol) in one portion at room temperature. Then 2-(trimethylsilyl) ethyloxy chloride (SEMCl) (0.48 mL, 2.6 mmol) was added in one portion and the mixture heated to reflux for 2 h. The reaction was cooled, diluted with EtOAc (20 mL) washed with water (10 mL), dried (MgSO4) and the solvent removed at reduced pressure. The residue was taken up in benzene (3 mL), applied to a plug of silica gel (10 g) and eluted with EtOAc/Hexane (1:3) until all the yellow color was washed from the silica gel plug. The solvent was evaporated and the residue taken on to the next step. This material was dissolved in dioxane (10 mL) and treated with K2CO3 (0.36 g, 2.6 mmol) in one portion. Then phenylchloroformate (0.27 mL, 2.23 mmol) was added in one portion and the reaction heated to 50 C for 2 h. The reaction was cooled and the solvent removed at reduced pressure. The residue was recrystalized from EtOH to give a

yellow solid (0.4 g, 43%). mp °C; CIMS m/e calculated for $C_{30}H_{32}N_3O_5Si$: 542.2111, found: 542.2101.

Step 2. Synthesis of Ex. I from 11.

Compound 11 (0.015 g, 0.03 mmol) in DMSO (0.2 mL) was treated with 3,5-dimethoxyphenylcarbazte (0.008 g, 0.06 mmol) in one portion and heated to 80 C for 30 minutes. The solvent was removed at reduced pressure heating to 65 C. The residue was disolved in EtOH (0.5 mL) and treated with 4N HCl/dioxane (0.4 mL). The mixture was heated to 80 C for 20 minutes and then cooled. The desired product was filtered and air dried (0.008g, 62%). mp >300 °C; CIMS m/e calculated for $C_{27}H_{24}N_5O_6(M+H^+)$: 514.1727, found: 514.1777.

Example II

Preparation of 3-(4-methoxyphenyl)-5-(2-isonicotinoylhydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-pyridylcarbazate as the starting material. mp 248 °C; CIMS m/e calculated for $C_{24}H_{19}N_6O_4(M+H^+)$: 455.1468, found: 455.1400.

Example III

Preparation of 3-(4-methoxyphenyl)-5-(2-nictinoylhydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3-pyridylcarbazate as the starting material. mp 227 °C; CIMS m/e calc'd for $C_{24}H_{19}N_6O_4(M+H^+)$: 455.1468, found: 455.1487.

Example IV

Preparation of 3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxy benzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3,4-dihydroxyphenyl carbazate as the starting material. mp >300 °C; CIMS m/e calc'd for $C_{25}H_{20}N_5O_6(M+H^+)$: 486.1414, found: 486.1497.

Example V

Preparation of 3-(4-methoxyphenyl)-5-(2-(4-hydroxy benzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-hydroxyphenyl carbazate as the starting material. mp 283 °C; CIMS m/e calc'd for $C_{25}H_{20}N_5O_5(M+H^+)$: 470.1464, found: 470.1544.

Example VI

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-aminobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3-aminophenyl carbazate as the starting material. mp 250 °C; CIMS m/e calc'd for $C_{25}H_{21}N_6O_4(M+H^+)$: 469.1624, found: 469.1513.

Example VII

Preparation of 3-(4-methoxyphenyl)-5-(2-(4-aminobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-aminophenyl carbazate as the starting material. mp 247 °C; CIMS m/e calc'd for $C_{25}H_{21}N_6O_4(M+H^+)$: 469.1624, found: 469.1528.

Example VIII

Preparation of 3-(4-methoxyphenyl)-5-(2-(2-aminobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2-aminophenyl carbazate as the starting material. mp 257 °C; CIMS m/e calc'd for $C_{25}H_{21}N_6O_4(M+H^+)$: 469.1624, found: 469.1548;

Example IX

Preparation of 3-(4-methoxyphenyl)-5-(2-(4-N,N-dimethylamino benzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-N,N-dimethylaminophenyl carbazate as the starting material. mp 259 °C; CIMS m/e calc'd for $C_{27}H_{25}N_6O_4(M+H^+)$: 497.1937, found: 497.1876.

Example X

Preparation of 3-(4-methoxyphenyl)-5-(2-methoxybenzoyl hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2-methoxyphenyl carbazate as the starting material. mp 269 °C; CIMS m/e calc'd for $C_{26}H_{22}N_5O_5(M+H^+)$: 484.1621, found: 484.1613.

Example XI

Preparation of 3-(4-methoxyphenyl)-5-(2-(2-hydroxy benzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2-hydroxyphenyl carbazate as the starting material. mp 280 °C; CIMS m/e calc'd for $C_{25}H_{20}N_5O_5(M+H^+)$: 470.1464, found: 470.1419.

Example XII

Preparation of 3-(4-methoxyphenyl)-5-(2-(3,5-diaminobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3,5-diaminophenyl carbazate as the starting material. mp >300 °C; CIMS m/e calc'd for $C_{25}H_{22}N_7O_4$(M+H$^+$): 484.1733, found: 484.1776.

Example XIII

Preparation of 3-(4-methoxyphenyl)-5-(2-(1-naphthoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 1-naphthhydrazide as the starting material. CIMS m/e calc'd for. $C_{29}H_{22}N_5O_4$(M+H$^+$): 504.1672, found: 504.1706.

Example XIV

Preparation of 3-(4-methoxyphenyl)-5-(2-amido hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using semicarbazide as the starting material. CIMS m/e calc'd for $C_{19}H_{17}N_6O_4$(M+H$^+$): 393.1311, found: 393.1333.

Example XV

Preparation of 3-(4-methoxyphenyl)-5-(2-phenylamido hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-phenylsemicarbazide as the starting material. CIMS m/e calc'd for $C_{25}H_{21}N_6O_4$(M+H$^+$): 469.1624, found: 469.1681.

Example XVI

Preparation of 3-(4-methoxyphenyl)-5-(2-(4-methylbenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-methylphenyl carbazate as the starting material. CIMS m/e calc'd for $C_{26}H_{22}N_5O_4(M+H^+)$: 468.1672, found: 468.1688.

Example XVII

Preparation of 3-(4-methoxyphenyl)-5-(2-(2-naphthoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2-naphthhadrazide as the starting material. CIMS m/e calc'd for $C_{29}H_{22}N_5O_4(M+H^+)$: 504.1672, found: 504.1710.

Example XVIII

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-(4-hydroxyphenyl)propionyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-hydroxyhydrocinamic acid hydrazide as the starting material. CIMS m/e calc'd for $C_{27}H_{24}N_5O_5(M+H^+)$: 498.1777, found: 498.1711.

Example XIX

Preparation of 3-(4-methoxyphenyl)-5-(2-(4-methoxybenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 4-methoxybenzhydrazide as the starting material. CIMS m/e calc'd for $C_{26}H_{22}N_5O_5(M+H^+)$: 484.1621, found: 484.1600.

Example XX

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3-nitrobenzhydrazide as the starting material. CIMS m/e calc'd for $C_{25}H_{19}N_6O_6(M+H^+)$: 499.1366, found: 499.1304.

Example XXI

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3,4,5-trimethoxybenzhydrazide as the starting material. CIMS m/e calc'd for $C_{28}H_{26}N_5O_7(M+H^+)$: 544.1832, found: 544.1812.

Example XXII

Preparation of 3-(4-methoxyphenyl)-5-(2-(2-thienoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2-thenoic hydrazide as the starting material. CIMS m/e calc'd for $C_{23}H_{18}N_5O_4S(M+H^+)$: 460.1080, found: 460.1012.

Example XXIII

Preparation of 3-(4-methoxyphenyl)-5-(2-(3-methylbenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3-methylbenzoic acid hydrazide as the starting material. CIMS m/e calc'd for $C_{26}H_{22}N_5O_4(M+H^+)$: 468.1672, found: 468.1640.

Example XXV

Preparation of 3-(4-methoxyphenyl)-5-(2-(2,5-dichlorobenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 2,5-dichlorobenzoic acid hydrazide as the starting material. CIMS m/e calc'd for $C_{25}H_{18}N_5O_4Cl_2$(M+H$^+$): 522.0736, found: 522.0777.

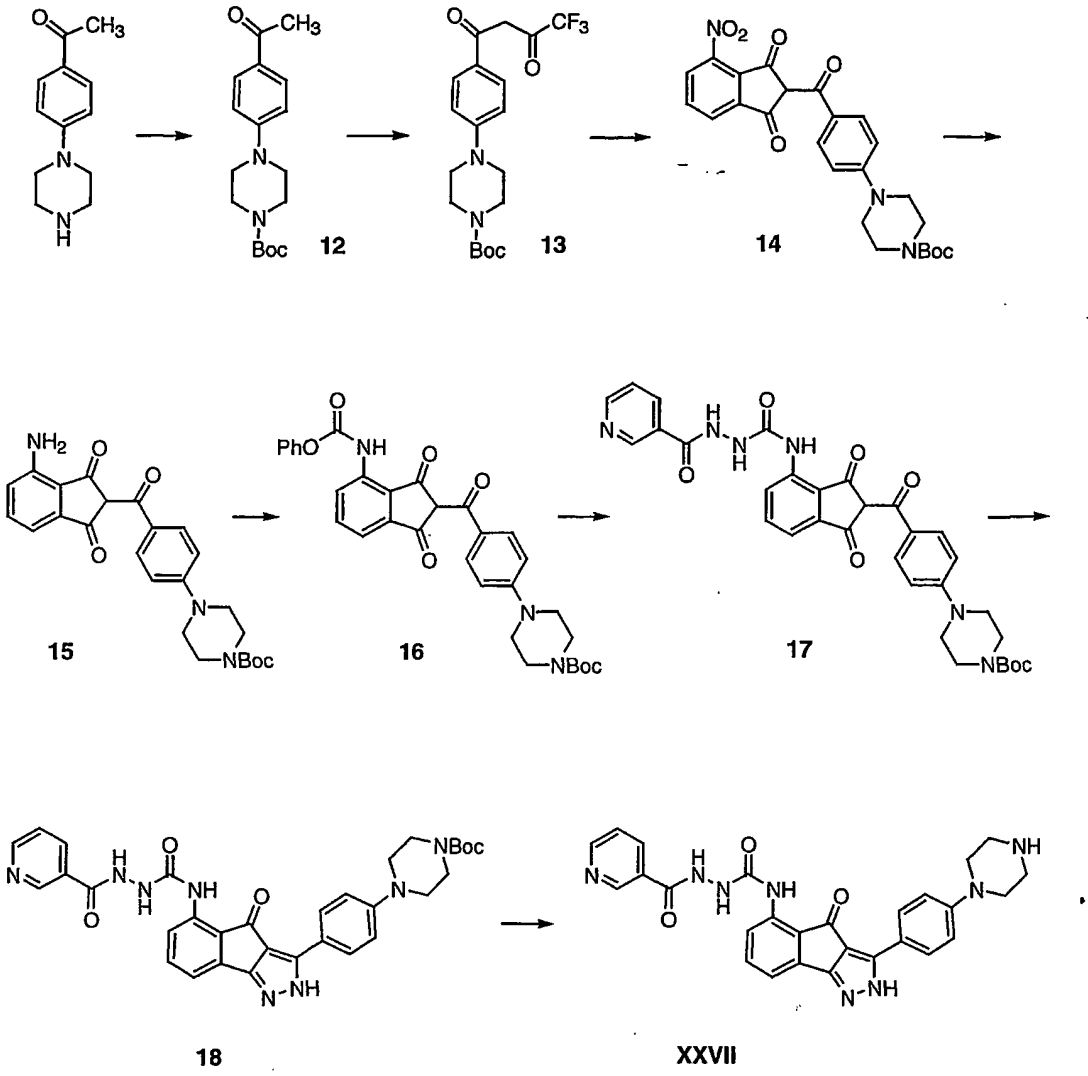
Example XXVI

Preparation of 3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example I using 3,4-dihydroxybenzoic acid hydrazide as the starting material. CIMS m/e calc'd for $C_{25}H_{20}N_5O_6$(M+H$^+$): 486.1414, found: 486.1445.

Example XXVII

Preparation of 3-(4-piperazinylphenyl)-5-(2-(nicotinoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one



Step 1. Preparation of 12

To a suspension of 139g (680 mmol) of 4-piperazinoacetophenone in 700mL of tetrahydrofuran at 25°C was added slowly over 20 min. a solution of 157g (720 mmol) of di-tert-butyl dicarbonate in 300mL of tetrahydrofuran. The resulting mixture was refluxed for 15h. After cooling the mixture was filtered, and the filtrate was concentrated under vacuum to provide an off-white solid. This crude product was recrystallized from diethyl ether/hexane to

afford 192g of the 12 as a white solid. NMR ($CDCl_3$) δ 7.89 (d, 2 H, J = 9 Hz), 6.87 (d, 2 H, J = 9 Hz), 3.59 (m, 4 H), 3.33 (m, 4 H), 2.53 (s, 3 H), 1.49 (s, 9 H).

Step 2. Preparation of 13 from 12

To a solution of 192g (630 mmol) of 12 and 90mL (750 mmol) of ethyl trifluoroacetate in 1000 mL of tetrahydrofuran at 25 °C was added slowly over 15 min. 280 mL (750 mmol) of 21% sodium ethoxide in ethanol, and the resulting solution then was stirred at 25°C for 16 h. The reaction mixture was diluted with 500mL of water, and to this mixture was added 45mL of acetic acid. The resulting precipitate was recovered by filtration. The solids were washed with diethyl ether/hexane and dried to furnish 236g of 13 as an orange solid. NMR ($CDCl_3$) δ 7.87 (d, 2 H, J = 9 Hz), 6.87 (d, 2 H, J = 9 Hz), 6.45 (s, 1 H), 3.60 (m, 4 H), 3.41 (m, 4 H), 1.48 (s, 9 H).

Step 3. Preparation of 14 from 13

A suspension of 117g (610 mmol) of 3-nitrophthalic anhydride in 560mL of acetic anhydride was heated until the mixture became homogeneous, and the solution then was allowed to cool to room temperature. To this solution was added 236g (590 mmol) of 13. The resulting mixture was cooled to 0°C, and 165mL (1200 mmol) of triethylamine was added slowly over 10 min. The mixture was allowed to warm to 25°C, was stirred at 25°C for 1h, and then was heated to 65°C for 0.5h. After cooling to room temperature, the reaction mixture was poured into a well-stirred solution of 1200mL of 1.0 N hydrochloric acid and 2000mL of ethanol. The resulting precipitate was recovered by filtration, washed with ethanol, and dried to provide 140g of 14 as an orange solid. NMR (acetone-d_6) δ 8.34 (d, 2H, J = 9 Hz), 8.05 (m, 3H), 7.07 (d, 2H, J = 9 Hz), 3.59 (br s, 8H), 1.48 (s, 9H).

Step 4. Preparation of 15 from 14

To a solution of 12.00g (25 mmol) of 14 in 500mL of ethanol and 50mL of conc. ammonium hydroxide at 25°C was added 500mL of water, followed by 15.3g (88 mmol) of sodium dithionite. The resulting mixture was stirred at 25°C for 16h. The reaction mixture was filtered, and the filtrate was reduced to ~1/2 the original volume under vacuum. This solution was adjusted to pH 3 employing hydrochloric acid and then extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over anhyd. sodium sulfate, filtered, and concentrated. The resulting solids were recrystallized from ethanol/water to provide 8.40g of 15 as a green solid. NMR (DMSO-d_6) δ 8.20 (d, 2H, J = 9 Hz), 7.44 (t, 1H, J = 8 Hz), 7.02 (d, 2H, J = 9 Hz), 6.96 (d, 1H, J = 8 Hz), 6.91 (d, 1H, J = 8 Hz), 6.70 (br s, 2H), 3.46 (br s, 8H), 1.43 (s, 9H).

Step 5. Preparation of 16 from 15

To a mixture of 7.05g (15.6 mmol) of 15, 8.67g (63 mmol) of potassium carbonate, 250mL of acetone at 25°C was added 2.40mL of phenyl chloroformate, and the resulting mixture was stirred at 25°C for 20h. The mixture was diluted with 500mL of water, adjusted to pH 3 employing hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over anhyd, sodium sulfate, filtered, and dried. The crude product was recrystallized from ethanol/water to afford 6.32g of 16 as a dark yellow solid. Mass Spec: m/e = 582 $(M-H)^-$.

Step 6. Preparation of 18 from 16

A solution of 0.57g (1.0 mmol) of 16 and 0.41g (3.0 mmol) of nicotinic acid hydrazide in 20mL of DMSO was stirred at 90°C for 2h. After cooling the solvent was removed under high vacuum to afford crude 17.

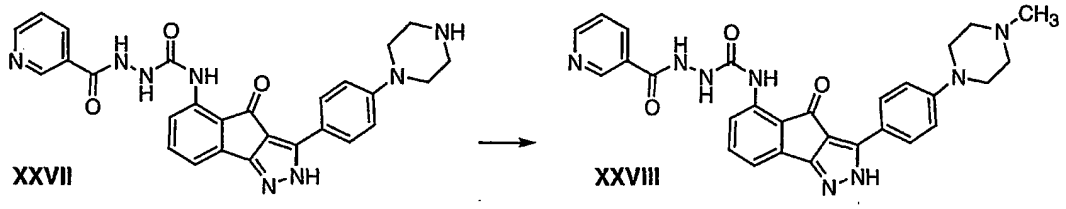
A solution of the crude 17, 0.10mL (2.0 mmol) of hydrazine hydrate, and 0.014g (0.2 mmol) of hydrazine hydrochloride in 20mL of ethanol was refluxed for 20h. While still at reflux the reaction mixture was diluted by dropwise addition of 10mL of water at a rate such that the refluxing of the solution was continuous. The mixture was allowed to cool to room temperature, and the resulting precipitate was recovered by filtration, washed with 95% ethanol, and dried to provide 0.25g of 18 as a yellow solid.

Step 7. Preparation of XXVII from 18

A solution of 0.25g (0.4 mmol) of 18 in 10mL of trifluoroacetic acid was stirred at 25°C for 2h. The excess trifluoroacetic acid was removed under vacuum, and the residue was dissolved in 20mL of hot ethanol. After cooling, the resulting precipitate was recovered by filtration under nitrogen and then dried under vacuum to afford 0.16g of the desired product as its trifluoroacetate salt. mp 232 °C; CIMS m/e calc'd for $C_{27}H_{25}N_8O_3(M+H^+)$: 509.2050, found: 509.2060.

Example XXVIII

Preparation of 3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(nicotinoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one



XXVII XXVIII

To a solution of 0.16g (0.26 mmol) of XXVII in 15mL of methanol and 5mL of water at 25°C was added sequentially 0.77g (9.5 mmol) of 37% aqueous formaldehyde, 0.32g (5.1 mmol) of sodium cyanoborohydride, and 3 drop of acetic acid. The resulting solution was stirred for 16h at 25°C. The solution was made acidic (pH<1) with conc. hydrochloric acid and was stirred for 20 min. until gas evolution ceased. The solution then was made basic (pH.13) with 50% aqueous sodium hydroxide solution. The mixture was stirred for 20 min, and then was adjusted to pH 9 with hydrochloric acid. The resulting precipitate was recovered by filtration, washed with 95% ethanol, and dried under vacuum. The yellow solid thus obtained was dissolved in 2mL of trifluoroacetic acid, and the solution was diluted with 10mL of hot anhydrous ethanol. Upon cooling a precipitate formed. This solid was recovered by filtration and dried under vacuum to afford 0.08g of the desired product as its trifluoroacetate salt. mp 238 °C; CIMS m/e calc'd for $C_{28}H_{27}N_8O_3(M+H^+)$: 523.2206, found: 523.2210.

Example XXIX

Preparation of 3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(isonicotinoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared from example XXX in a similar fashion as described for example XXVIII. mp 240 °C; CIMS m/e calc'd for $C_{28}H_{27}N_8O_3(M+H^+)$: 523.2206, found: 523.2208.

Example XXX

Preparation of 3-(4-piperazinylphenyl)-5-(2-(isonicotinoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example XXVII using isonicotinic acid hydrazide as the starting material. mp 232 °C; CIMS m/e calc'd for $C_{27}H_{25}N_8O_3(M+H^+)$: 509.2050, found: 509.2065.

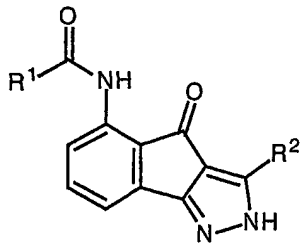
Example XXXI

Preparation of 3-(4-piperazinylphenyl)-5-(2-(3,5-dimethoxybenzoyl)hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one

Prepared in a similar fashion as described for example XXVII using 3,5-dimethoxybenzoic hydrazide as the starting material. mp >300 °C; CIMS m/e calc'd for $C_{30}H_{30}N_7O_5(M+H^+)$: 568.2309, found: 568.2316.

5

Table 1



Example #	R^1-C(O)N(R^5)NH-	R^2	mass (M^+H)	mp (°C)
I	3,5-dimethoxy $C_6H_3C(O)NHNH$-	4-$MeOC_6H_4$-	514	>300
II	4-pyridylC(O)NHNH-	4-$MeOC_6H_4$-	455	248
III	3-pyridylC(O)NHNH-	4-$MeOC_6H_4$-	455	227
IV	3,4-dihydroxy- $C_6H_3C(O)NHNH$-	4-$MeOC_6H_4$-	486	>300
V	4-hydroxy- $C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	470	283
VI	3-amino-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	469	250
VII	4-amino-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	469	247
VIII	2-amino-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	469	257
IX	4-N,N-dimethylamino- $C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	497	259
X	2-MeO-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	484	269
XI	2-OH-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	470	280
XII	3,5-di-NH_2-C_6H_3C (O)NHNH-	4-$MeOC_6H_4$-	484	>300
XIII	1-naphthylC(O)NHNH-	4-$MeOC_6H_4$-	504	
XIV	$H_2NC(O)NHNH$-	4-$MeOC_6H_4$-	393	

XV	$C_6H_4HNC(O)NHNH$-	4-$MeOC_6H_4$-	469	
XVI	4-Me-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	468	
XVII	2-naphthylC(O)NHNH-	4-$MeOC_6H_4$-	504	
XVIII	4-OH-$C_6H_4CH_2CH_2C(O)NHNH$-	4-$MeOC_6H_4$-	498	
XIX	4-MeO-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	484	
XX	2-NO_2-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	499	
XXI	3,4,5-tri-MeO-$C_6H_2C(O)NHNH$-	4-$MeOC_6H_4$-	544	
XXII	2-thienylC(O)NHNH-	4-$MeOC_6H_4$-	460	
XXIII	3-Me-$C_6H_4C(O)NHNH$-	4-$MeOC_6H_4$-	468	
XXIV	3-NH_2-4-OH-$C_6H_3C(O)NHNH$-	4-$MeOC_6H_4$-	485	
XXV	2,5-di-Cl-$C_6H_3C(O)NHNH$-	4-$MeOC_6H_4$-	522	
XXVI	3,4-di-OH-$C_6H_3C(O)NHNH$-	4-$MeOC_6H_4$-	486	
XXVII	3-pyridylC(O)NHNH-	4-piperazinyl C_6H_4-	509	232
XXVIII	3-pyridylC(O)NHNH-	4-(4-Me-piperazinyl) C_6H_4-	523	238
XXIX	4-pyridylC(O)NHNH-	4-(4-Me-piperazinyl) C_6H_4-	523	240
XXX	4-pyridylC(O)NHNH-	4-piperazinyl C_6H_4-	509	232
XXXI	3,5-di-MeO-$C_6H_3C(O)NHNH$-	4-piperazinyl C_6H_4-	568	>300

The compounds useful according to the invention optionally are supplied as salts. Those salts which are pharmaceutically acceptable are of particular interest since they are useful in administering the foregoing compounds for medical purposes. Salts which are not pharmaceutically acceptable are useful in manufacturing processes, for isolation and purification purposes, and in some instances, for use in separating stereoisomeric forms of the compounds of this invention. The latter is particularly true of amine salts prepared from optically active amines.

Where the compound useful according to the invention contains a carboxy group, or a sufficiently acidic bioisostere, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form.

Also, where the compound useful according to the invention contains a basic group, or a sufficiently basic bioisostere, acid addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form.

The foregoing compounds useful according to the invention may also be mixed another therapeutic compound to form pharmaceutical compositions (with or without diluent or carrier) which, when administered, provide simultaneous administration of a combination of active ingredients resulting in the combination therapy of the invention.

While it is possible for the compounds useful according to the invention to be administered alone it is preferably to present them as pharmaceutical compositions. The pharmaceutical compositions, both for veterinary and for human use, useful according to the present invention comprise at lease one compound of the invention, as above

defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients.

In certain preferred embodiments, active ingredients necessary in combination therapy may be combined in a single pharmaceutical composition for simultaneous administration.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the active compound, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the oily phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the emulsifying wax, and the way together with the oil and fat make up the emulsifying ointment base which forms the oily dispersed phase of a cream formulation. Emulgents and emulsion stabilizers

suitable for use in the formulation of the present invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

If desired, the aqueous phase of the cream base may include, for example, a least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogue.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used. Solid compositions of may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols, and the like.

The pharmaceutical compositions can be administered in a suitable formulation to humans and animals by topical or systemic administration, including oral, inhalational, rectal, nasal, buccal, sublingual, vaginal, parenteral

(including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), intracisternal and intraperitoneal. It will be appreciated that the preferred route may vary with for example the condition of the recipient.

The formulations can be prepared in unit dosage form by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tables may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compounds moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of the invention.

If desired, and for more effective distribution, the compounds can be microencapsulated in, or attached to, a slow release or targeted delivery systems such as a biocompatible, biodegradable polymer matrices (e.g. poly(d,l-lactide co-glycolide)), liposomes, and microspheres and subcutaneously or intramuscularly injected by a

technique called subcutaneous or intramuscular depot to provide continuous slow release of the compound(s) for a period of 2 weeks or longer. The compounds may be sterilized, for example, by filtration through a bacteria retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Actual dosage levels of active ingredient in the compositions of the invention may be varied so as to obtain an amount of active ingredient that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors.

Total daily dose of the compounds useful according to this invention administered to a host in single or divided doses may be in amounts, for example, of from about 0.001 to about 100 mg/kg body weight daily and preferably 0.01 to 10 mg/kg/day. Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the body weight, general health, sex, diet, time and route of administration, rates of absorption and excretion, combination with other drugs and the severity of the particular disease being treated.

The amount of each component administered is determined by the attending clinicians taking into consideration the etiology and severity of the disease, the patient's condition and age, the potency of each component and other factors.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials

with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Administration of a compound of the present invention in combination with additional therapeutic agents, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. The combination of a compound of the present invention with such additional therapeutic agents is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the therapeutic effect of the compound and agent when administered in combination is greater than the additive effect of the either the compound or agent when administered alone. In general, a synergistic effect is most clearly demonstrated at levels that are (therapeutically) sub-optimal for either the compound of the present invention or a known anti-proliferative agent alone, but which are highly efficacious in combination. Synergy can be in terms of improved inhibitory response without substantial increases in toxicity over individual treatments alone, or some other beneficial effect of the combination compared with the individual components.

The compounds of the invention, their methods or preparation and their biological activity will appear more clearly from the examination of the following examples which are presented as an illustration only and are not to be considered as limiting the invention in its scope.

Procedures for evaluating the biological activity of compounds or compositions according to the invention are carried out as described herein or by the application or adaptation of known procedures, by which is meant procedures used heretofore or as described in the literature.

UTILITY

Inhibition of Kinase/Cyclin Complex Enzymatic Activity

Several of the compounds disclosed in this invention were assayed for their inhibitory activity against cdk4/D1 and cdk2/E kinase complexes. Briefly, the in vitro assays employ cell lysates from insect cells expressing either of the kinases and subsequently their corresponding regulatory units. The cdk2/cyclinE is purified from insect cells expressing His-tagged cdk2 and cyclin E. The cdk/cyclin lysate is combined in a microtitre-type plate along with a kinase compatible buffer, ^{32}P-labeled ATP at a concentration of 50 mM, a GST-Rb fusion protein and the test compound at varying concentrations. The kinase reaction is allowed to proceeded with the radiolabled ATP, then effectively stopped by the addition of a large excess of EDTA and unlabeled ATP. The GST-Rb labeled protein is sequestered on a GSH-Sepharose bead suspension, washed, resuspended in scintillant, and the ^{32}P activity detected in a scintillation counter. The compound concentration which inhibits 50% of the kinase activity was calculated for each compound. A compound was considered active if its IC_{50} was found to be less than 1 μM.

Inhibition of HCT 116 Cancer Cell Proliferation

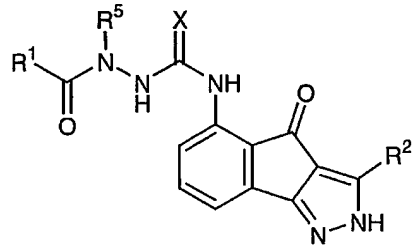
To test the cellular activity of several compounds disclosed in this invention, we examined the effect of these compounds on cultured HCT116 cells and determined their effect on cell-cycle progression by the colorimetric

cytotoxcity test using sulforhodamine B (Skehan et al. J. Natl. Cancer Inst. 82:1107-12, 1990). Briefly, HCT116 cells are cultured in the presence of test compounds at increasing concentrations. At selected time points, groups of cells are fixed with trichloroacetic acid and stained with sulforhodamine B (SRB). Unbound dye was removed by washing and protein-bound dye was extracted for determination of optical density. A compound was considered active if its IC_{50} was found to be less than 10 μM.

CLAIMS

What is claimed is:

1. A compound of formula (I):



X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C_{1-4} alkyl substituted with 1-3 R^4, C_{5-10} alkyl substituted with 0-3 R^4, C_2-C_{10} alkenyl substituted with 0-3 R^4, C_2-C_{10} alkynyl substituted with 0-3 R^4, C_3-C_{10} carbocycle substituted with 0-5 R^6, or 5-10 membered heterocycle substituted with 0-3 R^6;

provided that if R^1 is phenyl or benzyl, then R^1 is substituted with 1-5 R^6;

R^2 is H, C_{1-10} alkyl substituted with 0-3 R^7, C_{2-10} alkenyl substituted with 0-3 R^7, C_{2-10} alkynyl substituted with 0-3 R^7, $-CF_3$, C_{3-10} carbocycle substituted with 0-5 R^8, or 3-10 membered heterocycle substituted with 0-5 R^8;

R^3 and R^{3a} are independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^4 and R^7 are, at each occurance, independently selected from the group: halo, -CN, NO_2, $-NR^9R^{9a}$, $NR^9NR^{9a}R^{9b}$, $NR^9C(O)OR^{10}$, $NR^9C(O)R^{10}$, =O, OR^{10}, SR^{10}, -CF3, COR^{10},

CO_2R^{10}, $CONR^9R^{9a}$, $NHC(O)NR^9R^{9a}$, $NHC(S)NR^9R^{9a}$, $SO_2NR^9R^{9a}$, SO_2R^{10}, C_{3-10} carbocycle substituted with 0-5 R^{11}, and 5-10 membered heterocycle substituted with 0-3 R^{11};

R^5 is selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^6 and R^8 are, at each occurance, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, SO_2R^{14}, C_{3-10} carbocycle substituted with 0-5 R^{15}, and 5-10 membered heterocycle substituted with 0-3 R^{15}, or when two R^{6s} or R^{8s} are attachd to two adjacent carbon atoms, the two R^{6s} or R^{8s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$;

R^9 is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{9b} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl; or

R^9 and R^{9a}, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R^{16};

R^{9a} is selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{10}, R^{14}, R^{17} are, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl, benzyl;

R^{11} is, at each occurance, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{18}R^{18a}$, $NR^{18}NR^{18a}R^{18b}$, $NR^{18}C(O)OR^{17}$, $NR^{18}C(O)R^{17}$, =O, OR^{17}, SR^{17}, COR^{17}, CO_2R^{17}, $CONR^{18}R^{18a}$, $NHC(O)NR^{18}R^{18a}$, $NHC(S)NR^{18}R^{18a}$, $SO_2NR^{18}R^{18a}$, SO_2R^{17}, C_{3-10} carbocycle substituted with 0-5 R^{19}, and 5-10 membered heterocycle substituted with 0-3 R^{19};

R^{13} is is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{13a} is, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; or

R^{13} and R^{13a}, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R^{16};

R^{13b} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{15}, R^{16} and R^{19} are, at each occurance, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{20}R^{20a}$, $NR^{20b}NR^{20}R^{20a}$, $NR^{20}C(O)OR^{21}$, $NR^{20}C(O)R^{21}$, =O, OR^{21}, SR^{21}, COR^{21}, CO_2R^{21}, $CONR^{20}R^{20a}$, $NHC(O)NR^{20}R^{20a}$, $NHC(S)NR^{20}R^{20a}$, $SO_2NR^{20}R^{20a}$, SO_2R^{21}, or when two R^{15}s, R^{16}s or R^{19}s are attachd to two adjacent

carbon atoms, the two R^{15}s R^{16}s or R^{19}s may combine to form -OCH2O- or -OCH2CH2O-;

R^{18} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{18a} is, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;or

R^{18} and R^{18a}, together with the nitrogen atom to which they are attached, form a heterocycle substituted with 0-3 R^{19};

R^{18b} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl; or

R^{20} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl;

R^{20a} is, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{20b} is, at each occurance, independently selected from the group: H, $-C(O)R^{12}$, $-C(O)OR^{12}$, C_{1-4} alkyl, phenyl and benzyl; and

R^{12} and R^{21} are, at each occurance, independently selected from the group: H, C_{1-4} alkyl, phenyl, benzyl; or

a pharmaceutically acceptable salt form thereof, a pharmaceutically acceptable prodrug form thereof, an N-oxide form thereof, or a stereoisomer thereof.

2. A compound accoding to claim 1 wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4, C_2-C_4 alkenyl substituted with 0-3 R^4, C_2-C_4 alkynyl substituted with 0-3 R^4, C_3-C_{10} carbocycle substituted with 0-5 R^6, or 5-10 membered heterocycle substituted with 0-3 R^6.

3. A compound accoding to claim 1 wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4, C_2-C_4 alkenyl substituted with 0-3 R^4, C_2-C_4 alkynyl substituted with 0-3 R^4, C_3-C_6 carbocycle substituted with 0-5 R^6, or 5-7 membered heterocycle substituted with 0-3 R^6.

4. A compound accoding to claim 1 wherein:

R^1 is C_3-C_6 saturated carbocycle substituted with 0-5 R^6, or 5-7 membered saturated heterocycle substituted with 0-3 R^6.

5. A compound accoding to claim 1 wherein:

R^1 is C_5-C_6 partially saturated carbocycle substituted with 0-5 R^6, or 5-7 membered partially saturated heterocycle substituted with 0-3 R^6.

6. A compound accoding to claim 1 wherein:

R^1 is phenyl substituted with 1-5 R^6, naphthyl substituted with 0-5 R^6, or 5-6 membered aromatic heterocycle substituted with 0-3 R^6.

7. A compound accoding to claim 1 wherein:

R^1 is phenyl substituted with 1-3 R^6, naphthyl substituted with 0-3 R^6, or 5-6 membered aromatic heterocycle substituted with 0-3 R^6.

8. A compound accoding to claim 1 wherein:

R^1 is C_3-C_{10} carbocycle substituted with 0-5 R^6, or 5-10 membered heterocycle substituted with 0-3 R^6;

R^6 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14}, or when two R^{6s} are attached to two adjacent carbon atoms, the two R^{6s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$.

9. A compound accoding to claim 1 wherein:

R^6 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14}, or when two R^{6s} are attached to two adjacent carbon atoms, the two R^{6s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$;

R^{13}, R^{13a} and R^{13b} are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; and

R^{14} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl, and benzyl.

10. A compound accoding to claim 1 wherein:

R^6 is independently at each occurrence selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14};

R^{13}, R^{13a} and R^{13b} are each independently selected from the group: H or methyl;and

R^{14} is independently selected from the group: H, methyl, phenyl, and benzyl.

11. A compound accoding to claim 1 wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4;

R^4 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, $-NR^9R^{9a}$, $NR^9NR^{9a}R^{9b}$, $NR^9C(O)OR^{10}$, $NR^9C(O)R^{10}$, =O, OR^{10}, SR^{10}, -CF3, COR^{10}, CO_2R^{10}, $CONR^9R^{9a}$, $NHC(O)NR^9R^{9a}$, $NHC(S)NR^9R^{9a}$, $SO_2NR^9R^{9a}$, and SO_2R^{10};

R^9 is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9a} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9b} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; or

R^9 and R^{9a}, together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3 R^{16};

R^{16} is, at each occurrence, independently selected from the group consisting of: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{20}R^{20a}$, $NR^{20b}NR^{20}R^{20a}$, $NR^{20}C(O)OR^{21}$, $NR^{20}C(O)R^{21}$, =O, OR^{21}, SR^{21}, COR^{21}, CO_2R^{21}, $CONR^{20}R^{20a}$, $NHC(O)NR^{20}R^{20a}$, $NHC(S)NR^{20}R^{20a}$, $SO_2NR^{20}R^{20a}$, and SO_2R^{21}; and

R^{20}, R^{20a}, and R^{20b} are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl.

12. A compound accoding to claim 1 wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4;

R^3 and R^{3a} are independently selected from the group: H, methyl, phenyl and benzyl;

R^4 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, $-NR^9R^{9a}$, $NR^9NR^{9a}R^{9b}$, $NR^9C(O)OR^{10}$, $NR^9C(O)R^{10}$, =O, OR^{10}, SR^{10}, -CF3, COR^{10}, CO_2R^{10}, $CONR^9R^{9a}$, $NHC(O)NR^9R^{9a}$, $NHC(S)NR^9R^{9a}$, $SO_2NR^9R^{9a}$, SO_2R^{10}, C_{3-10} carbocycle substituted with

0-5 R^{11}, and 5-10 membered heterocycle substituted with 0-3 R^{11};

R^9 is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9a} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9b} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{10} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl, benzyl; and

R^{11} is, at each occurrence, independently selected from the group consisting of: selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{18}R^{18a}$, $NR^{18}NR^{18a}R^{18b}$, $NR^{18}C(O)OR^{17}$, $NR^{18}C(O)R^{17}$, =O, OR^{17}, SR^{17}, COR^{17}, CO_2R^{17}, $CONR^{18}R^{18a}$, $NHC(O)NR^{18}R^{18a}$, $NHC(S)NR^{18}R^{18a}$, $SO_2NR^{18}R^{18a}$, SO_2R^{17}, C_{3-10} carbocycle substituted with 0-5 R^{19}, and 5-10 membered heterocycle substituted with 0-3 R^{19}.

13. A compound accoding to claim 1 wherein:

R^2 is C_{1-4} alkyl substituted with 0-3 R^7, C_{2-4} alkenyl substituted with 0-3 R^7, C_{2-4} alkynyl substituted with 0-3 R^7, $-CF_3$, C_{3-6} carbocycle substituted with 0-5 R^8, or 3-7 membered heterocycle substituted with 0-5 R^8.

14. A compound accoding to claim 1 wherein:

R^2 is C_{1-4} alkyl substituted with 0-3 R^7, C_{2-4} alkenyl substituted with 0-3 R^7, C_{2-4} alkynyl substituted with 0-3 R^7, $-CF_3$, C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8.

15. A compound accoding to claim 1 wherein:

R^2 is C_{3-6} saturated carbocycle substituted with 0-5 R^8, or 5-7 membered saturated heterocycle substituted with 0-5 R^8.

16. A compound accoding to claim 1 wherein:

R^2 is C_{5-6} partially saturated carbocycle substituted with 0-5 R^8, or 5-7 membered partially saturated heterocycle substituted with 0-5 R^8.

17. A compound accoding to claim 1 wherein:

R^2 is phenyl substituted with 0-5 R^8, naphthyl substituted with 0-5 R^8 or or 5-6 membered aromatic heterocycle heterocycle substituted with 0-5 R^8.

18. A compound accoding to claim 1 wherein:

R^2 is phenyl substituted with 0-3 R^8, naphthyl substituted with 0-3 R^8 or or 5-6 membered aromatic heterocycle heterocycle substituted with 0-3 R^8.

19. A compound accoding to claim 1 wherein:

R^2 is C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8;

R^8 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14}, or when two R^{8s} are attachd to two adjacent carbon atoms, the two R^{8s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$; and

R^{13} R^{13a}, and R^{13b} are are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; or

R^{13} and R^{13a}, together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3 R^{16}.

20. A compound accoding to claim 1 wherein:

R^2 is C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8;

R^8 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, SO_2R^{14}, C_{3-10} carbocycle substituted with 0-5 R^{15}, and 5-10

membered heterocycle substituted with 0-3 R^{15}, or when two R^{8s} are attachd to two adjacent carbon atoms, the two R^{8s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$;

R^{13} R^{13a}, and R^{13b} are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; and

R^{15} is, at each occurrence, independently selected from the group consisting of: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{20}R^{20a}$, $NR^{20b}NR^{20}R^{20a}$, $NR^{20}C(O)OR^{21}$, $NR^{20}C(O)R^{21}$, =O, OR^{21}, SR^{21}, COR^{21}, CO_2R^{21}, $CONR^{20}R^{20a}$, $NHC(O)NR^{20}R^{20a}$, $NHC(S)NR^{20}R^{20a}$, $SO_2NR^{20}R^{20a}$, and SO_2R^{21}, or when two R^{15}s, are attachd to two adjacent carbon atoms, the two R^{15}s may combine to form -OCH2O- or -OCH2CH2O-.

21. A compound accoding to claim 1 wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4, C_2-C_4 alkenyl substituted with 0-3 R^4, C_2-C_4 alkynyl substituted with 0-3 R^4, C_3-C_6 carbocycle substituted with 0-5 R^6, or 5-7 membered heterocycle substituted with 0-3 R^6; and

R^2 is C_{1-4} alkyl substituted with 0-3 R^7, C_{2-4} alkenyl substituted with 0-3 R^7, C_{2-4} alkynyl substituted with 0-3 R^7, $-CF_3$, C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8.

22. A compound accoding to claim 1 wherein:

R^1 is phenyl substituted with 1-5 R^6, naphthyl substituted with 0-5 R^6, or 5-6 membered aromatic heterocycle substituted with 0-3 R^6;

R^2 is C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8;

R^8 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{13}R^{13a}$, $NR^{13}NR^{13a}R^{13b}$, $NR^{13}C(O)OR^{14}$, $NR^{13}C(O)R^{14}$, =O, OR^{14}, SR^{14},-CF3, COR^{14}, CO_2R^{14}, $CONR^{13}R^{13a}$, $NHC(O)NR^{13}R^{13a}$, $NHC(S)NR^{13}R^{13a}$, $SO_2NR^{13}R^{13a}$, and SO_2R^{14}, or when two R^{8s} are attachd to two adjacent carbon atoms, the two R^{8s} may combine to form $-OCH_2O-$ or $-OCH_2CH_2O-$; and

R^{13} R^{13a}, and R^{13b} are are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; or

R^{13} and R^{13a}, together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3 R^{16}.

23. A compound accoding to claim 1 wherein:

X is O or S;

R^1 is $-NR^3R^{3a}$, $-CF_3$, C1-C4 alkyl substituted with 1-3 R^4;

R^2 is C_{1-4} alkyl substituted with 0-3 R^7, C_{2-4} alkenyl substituted with 0-3 R^7, C_{2-4} alkynyl substituted with

0-3 R^7, $-CF_3$, C_{3-6} carbocycle substituted with 0-5 R^8, or 5-7 membered heterocycle substituted with 0-5 R^8;

R^4 is, at each occurrence, independently selected from the group: halo, -CN, NO_2, $-NR^9R^{9a}$, $NR^9NR^{9a}R^{9b}$, $NR^9C(O)OR^{10}$, $NR^9C(O)R^{10}$, =O, OR^{10}, SR^{10}, -CF3, COR^{10}, CO_2R^{10}, $CONR^9R^{9a}$, $NHC(O)NR^9R^{9a}$, $NHC(S)NR^9R^{9a}$, $SO_2NR^9R^{9a}$, and SO_2R^{10};

R^9 is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9a} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl;

R^{9b} is, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl; or

R^9 and R^{9a}, together with the nitrogen atom to which they are attached, form a 5-7 membered heterocycle substituted with 0-3 R^{16};

R^{16} is, at each occurrence, independently selected from the group consisting of: halo, -CN, NO_2, C_{1-4} alkyl, C_{1-4} haloalkyl, $NR^{20}R^{20a}$, $NR^{20b}NR^{20}R^{20a}$, $NR^{20}C(O)OR^{21}$, $NR^{20}C(O)R^{21}$, =O, OR^{21}, SR^{21}, COR^{21}, CO_2R^{21}, $CONR^{20}R^{20a}$, $NHC(O)NR^{20}R^{20a}$, $NHC(S)NR^{20}R^{20a}$, $SO_2NR^{20}R^{20a}$, and SO_2R^{21}; and

R^{20}, R^{20a}, and R^{20b} are, at each occurrence, independently selected from the group: H, C_{1-4} alkyl, phenyl and benzyl.

24. A compound accoding to claim 1 selected from the group:

3-(4-methoxyphenyl)-5-(2-(3,5-dimethoxybenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-isonicotinoyl hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-nictinoylhydrazinecarbox amido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-hydroxybenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-aminobenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-aminobenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-aminobenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-N,N-dimethylaminobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-methoxybenzoylhydrazine carboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-hydroxybenzoyl)hydrazine carboxamido)indeno[1,2-c]pyrazol-4-one; and

3-(4-methoxyphenyl)-5-(2-(3,5-diaminobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(1-naphthoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-amido hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-phenylamido hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-methylbenzoyl hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-naphthoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-(4-hydroxyphenyl)propionyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(4-methoxybenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-nitrobenzoyl) hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2-thienoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-methylbenzoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3-amino-4-hydroxybenzoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(2,5-dichlorobenzoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-methoxyphenyl)-5-(2-(3,4-dihydroxybenzoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-piperazinylphenyl)-5-(2-(nicotinoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(nicotinoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-(4-methylpiperazinyl)phenyl)-5-(2-(isonicotinoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one;

3-(4-piperazinylphenyl)-5-(2-(isonicotinoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one; and

3-(4-piperazinylphenyl)-5-(2-(3,5-dimethoxybenzoyl)
hydrazinecarboxamido)indeno[1,2-c]pyrazol-4-one; or

a pharmaceutically acceptable salt form thereof, a pharmaceutically acceptable prodrug form thereof, an N-oxide form thereof, or a stereoisomer thereof.

25. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

26. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier, a compound according to claim 1 or a pharmaceutically acceptable salt or prodrug form thereof, and a cytostatic or cytotoxic agent.

27. A method of treating a cell proliferative disease associated with CDK activity in a patient in need thereof,comprising administrering to said patient a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein the proliferative diseases is selected from the group consisting of: Alzheimer's disease, viral infections, auto-immune diseases, fungal disease, cancer, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis, neurodegenerative disorders and post-surgical stenosis and restenosis.

28. A method of treating cancer associated with CDK activity in a patient in need thereof,comprising administrering to said patient a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein the cancer is selected from the group consisting of: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid,

prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

29. A method of treating a disease associated with apoptosis in a patient in need thereof, comprising administrering to said patient a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein the disease associated with apoptosis is selected from the group consisting of: cancer, viral infections, autoimmune diseases and neurodegenerative disorder.

30. A method of inhibiting tumor angiogenesis and metastasis in a patient in need thereof, comprising administrering to said patient a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

31. A method of modulating the level of cellular RNA and DNA synthesis in a patient in need thereof, comprising administering to said patient a CDK inhibitory effective

amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

32. A method of treating viral infections in a patient in need thereof, comprising administering to said patient a CDK inhibitory effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein the viral infections is selected from the group consiting of HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus.

33. A method of chemopreventing cancer in a patient, comprising administering to said patient in need thereof, a CDK inhibitory effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

34. A method of inhibiting CDK activity comprising combining an effective amount of a compound according to claim 1, with a composition containing CDK.

35. A method of treating cancer associated with CDK activity in a patient in need thereof,comprising administrering to said patient a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, wherein such agents are selected from the group consisting of: DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors,

such as 5-fluorouracil; and anti-metabolites, such as methoxtrexate.

36. A method treating cell proliferative diseases associated with CDK activity in a patient in need thereof, comprising administrering to said patient a pharmaceutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, in combination (administered together or sequentially) with known anti-proliferating agents selected from the group consisting of:, altretamine, busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, thiotepa, cladribine, fluorouracil, floxuridine, gemcitabine, thioguanine, pentostatin, methotrexate, 6-mercaptopurine, cytarabine, carmustine, lomustine, streptozotocin, carboplatin, cisplatin, oxaliplatin, iproplatin, tetraplatin, lobaplatin, JM216, JM335, fludarabine, aminoglutethimide, flutamide, goserelin, leuprolide, megestrol acetate, cyproterone acetate, tamoxifen, anastrozole, bicalutamide, dexamethasone, diethylstilbestrol, prednisone, bleomycin, dactinomycin, daunorubicin, doxirubicin, idarubicin, mitoxantrone, losoxantrone, mitomycin-c, plicamycin, paclitaxel, docetaxel, CPT-11, epothilones , topotecan, irinotecan, 9-amino camptothecan, 9-nitro camptothecan, GS-211, etoposide, teniposide, vinblastine, vincristine, vinorelbine, procarbazine, asparaginase, pegaspargase, methoxtrexate, octreotide, estramustine, and hydroxyurea.

37. A method of inhibiting CDK1 activity, comprising adminsitering to a patient in need thereof an efective CDK1 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

38. A method of inhibiting CDK2 activity, comprising adminsitering to a patient in need thereof an efective CDK2 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

39. A method of inhibiting CDK3 activity, comprising adminsitering to a patient in need thereof an efective CDK3 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

40. A method of inhibiting CDK4 activity, comprising adminsitering to a patient in need thereof an efective CDK4 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

41. A method of inhibiting CDK5 activity, comprising adminsitering to a patient in need thereof an efective CDK5 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

42. A method of inhibiting CDK6 activity, comprising adminsitering to a patient in need thereof an efective CDK6 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

43. A method of inhibiting CDK7 activity, comprising adminsitering to a patient in need thereof an efective CDK7 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

44. A method of inhibiting CDK8 activity, comprising adminsitering to a patient in need thereof, an efective CDK8 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

45. A method of inhibiting CDK9 activity, comprising adminsitering to a patient in need thereof an efective CDK9 inhibitory amount of a compound according to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof.

46. A pharmaceutical kit for treating a cell proliferative disease associated with CDK activity, said kit comprising a plurality of separate containers, wherein at least one of said containers contains a compound accordig to claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, and at least another of said containers contains one or more compounds selected from the group consisting of cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as carboplatin, cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, taxane, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methoxtrexate, and said containers optionally contain a pharmaceutical carrier, which kit may be effectively utilized for carrying out combination therapies according to the invention.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 00/28952

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/54 C07D401/12 C07D409/12 A61K31/416 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 54308 A (DU PONT PHARM CO) 28 October 1999 (1999-10-28) compounds LXIV, CIV - CXI, CXIII, CXIV, CL page 1, line 10 - line 15; claims 1,7	1-46

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2001	19/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "prodrug" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include prodrugs of the compounds of formula I.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ıtion on patent family members

Internat Application No
PCT/US 00/28952

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9954308 A	28-10-1999	AU 3654899 A	08-11-1999
		EP 1071668 A	31-01-2001